

A CONCISE SYNTHESIS OF (-)-*ENDO*-BREVICOMIN

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Abstract- A new method for the synthesis of (-)-*endo*-brevicomine from *D*-ribose in four steps is reported.

endo-Brevicomine¹ is the aggregation pheromone of different bark beetle species of the *Dendroctonus* and *Dryocoetes* family, with its (+)-enantiomer {(1*R*,5*S*,7*S*)-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane} being bioactive.² In connection with our ongoing program for the synthesis of enantiomerically pure pheromones³ and in addition to several asymmetric syntheses of both enantiomers of *endo*-brevicomine which appeared recently in the literature,⁴ we report herein a new concise synthesis of (-)-*endo*-brevicomine (**1**) (Figure 1), starting from *D*-ribose.

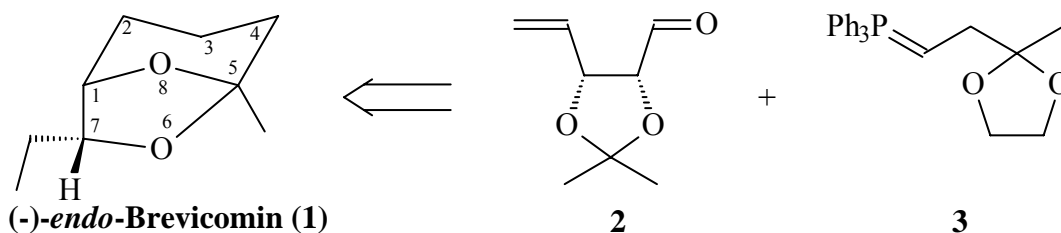
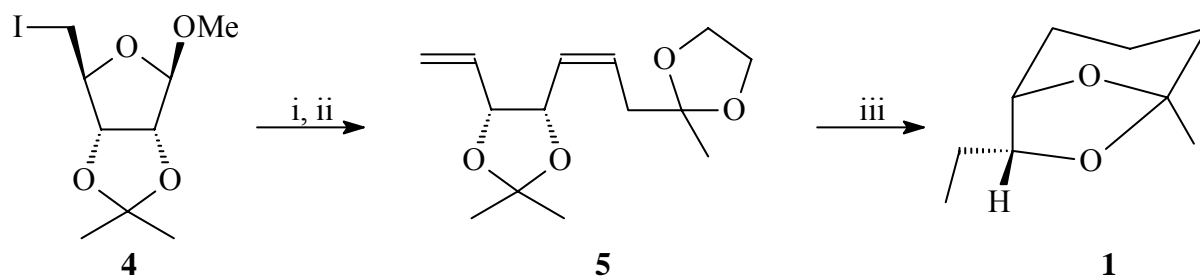


Figure 1

It is evident from Figure 1, that the configuration of the two chiral centers of (4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (**2**), easily accessible from *D*-ribose,⁵ is identical to those of C-1 and C-7 carbons of (-)-*endo*-brevicomine (**1**). Furthermore, aldehyde (**2**) has the proper skeleton size and functionalities to give the desired (-)-*endo*-brevicomine (**1**), upon Wittig olefination with the ylide (**3**),⁶ and subsequent conventional hydrogenation and reacetalisation. Evidently, its enantiomeric (+)-*endo*-brevicomine could be prepared by using the enantiomer of aldehyde (**2**), whereas the respective (+)- and (-)-*exo*-brevicomines could result from the olefination of ylide (**3**) with the two epimeric *threo*-isomers of aldehyde (**2**).

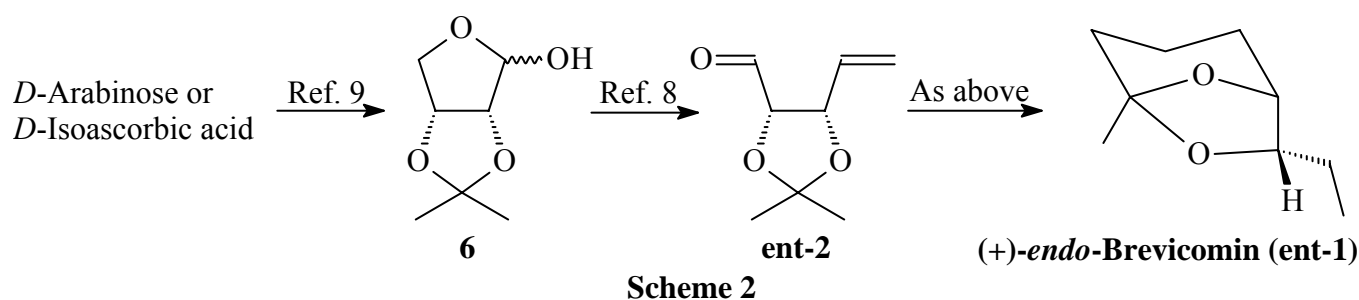
Iodide (**4**) (Scheme 1), obtained from *D*-ribose in two steps, was converted to aldehyde (**2**) by treatment with powdered Zn in refluxing ethanol, according to the literature.⁵ In our hands, aldehyde (**2**), thus prepared, was isolated by filtering off the solids and careful complete evaporation of the solvent in a

rotary evaporator at temperatures not exceeding 35 °C, to avoid coevaporation of the volatile aldehyde (**2**).⁷ Subsequent Wittig olefination with the ylide (**3**) gave compound (**5**) in 65% yield. Attempted H₂-Pd/C (10%) catalytic hydrogenation caused extended decomposition of **5**, whereas the hydrogenation of **5** over Raney Ni in ether, followed by treatment with *p*-toluenesulfonic acid and water gave good yield of (-)-*endo*-brevicomins (**1**), with physical and NMR spectral data identical to those reported in the literature.^{2,4}



Scheme 1 Reagents and Conditions: *i*, Zn powder, 95% EtOH, reflux, 1 h; *ii*, [2-(2-methyl-1,3-dioxolan-2-yl)ethyl](triphenyl)phosphonium bromide, 1.6 M *n*-BuLi in hexane, 12-crown-4, -78 °C, THF, 65% from **4**; *iii*, H₂, Raney Ni, ether, 20 °C, 5 h, then *p*-TsOH, H₂O, 20 °C, 3 h, 76% overall.

(4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (**ent-2**) (Scheme 2) is also readily prepared from protected *D*-erythrose (**6**) in two steps, namely Wittig olefination with Ph₃P=CH₂ and Swern oxidation of the resulting alcohol.⁸ *D*-Erythrose (**6**) in turn is easily available from the naturally abundant *D*-arabinose^{9a} or *D*-isoascorbic acid.^{9b} The synthesis thus of the biologically active (+)-*endo*-brevicomins (**ent-1**) can be accomplished when applying the reaction sequence of Scheme 1. It is evident that aldehyde (**2**) used in the synthesis of (-)-*endo*-brevicomins (**1**) can alternatively be obtained from *L*-arabinose.^{8,9}



In conclusion, we have developed a short method for the synthesis of (-)-*endo*-brevicomins (**1**) from aldehyde (**2**), easily accessible from *D*-ribose. Since the enantiomer of this aldehyde (**ent-2**) is also readily available from *D*-arabinose or *D*-isoascorbic acid, our method is suitable for the synthesis of both (+)- and (-)-*endo*-brevicomins.

EXPERIMENTAL

(4*S*,5*R*)-2,2-dimethyl-4-[(*Z*)-3-(2-methyl-1,3-dioxolan-2-yl)-1-propenyl]-5-vinyl-1,3-dioxolane (**5**). To a well stirred solution of **4**⁵ (0.314 g, 1 mmol) in EtOH 95% (5 mL) was added powdered Zn (0.65 g, 10

mmol) and the mixture was refluxed for 1 h, while the reaction progress was monitored by TLC. The solids were then filtered off and the solvent was carefully evaporated in a rotary evaporator under reduced pressure with the bath temperature not exceeding 35 °C. The resulting aldehyde (**2**) was of satisfactory purity and was used without any further purification.

In a separate flask, ylide (**3**) was prepared from [2-(2-methyl-1,3-dioxolan-2-yl)ethyl](triphenyl)phosphonium bromide⁶ (2.75 g, 6 mmol) in dry THF (150 mL) by adding dropwise 1.6 M of *n*-BuLi in hexane (4.1 mL, 6.6 mmol) at -78 °C in the presence of 12-crown-4 (0.211 g, 1.2 mmol). The mixture was then allowed to warm to 0 °C and cooled again to -78 °C. The above prepared aldehyde (**2**) was added at this temperature and the resulting solution was allowed overnight stirring to warm to rt, quenched by adding H₂O (100 mL) and extracted with EtOAc (100 mL). The aqueous layer was extracted again with CH₂Cl₂ (3x50 mL). The combined organic layer was dried over Na₂SO₄, the solvent was evaporated and the residue was chromatographed on silica gel using hexane/EtOAc 5:1 as the eluent to give compound (**5**) as an oil (0.165 g, 65%); [α]_D²⁷ +28.6 ° (c 0.12, CHCl₃); δ _H (CDCl₃, 300 MHz) 1.31 (s, 3 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 2.44 (d, *J* 7.7, 2 H), 3.94 (br s, 4 H), 4.57 (t, *J* 6.5, 1 H), 4.95 (dd, *J* 9.0, 6.5, 1 H), 5.20 (d, *J* 11.2, 1 H), 5.29 (d, *J* 16.9, 1 H), 5.54 (dd, *J* 10.8, 9.0, 1 H), and 5.75 (m, 2 H); δ _C (CDCl₃, 75 MHz) 20.08, 25.53, 28.04, 37.45, 64.71, 74.22, 79.75, 108.65, 109.35, 117.76, 128.38, 128.46, and 134.42; Anal. Calcd for C₁₄H₂₂O₄: C, 66.12; H, 8.72. Found: C, 65.98; H, 8.84.

(-)-*endo*-Brevicomine (**1**). To a solution of compound (**5**) obtained as above (0.127 g, 0.5 mmol) in ether (20 mL) was added Raney Ni (5 mg) and the mixture was stirred at rt under 1 atm H₂ at 20 °C for 5 h. The solids were filtered off, *p*-TsOH·H₂O (10 mg, 0.05 mmol) and H₂O (1 mL) were added and the mixture was stirred at 20 °C for 3 h and then washed with 10% aqueous Na₂CO₃ (20 mL) and H₂O (20 mL) and dried over Na₂SO₄. The solvent was evaporated under atmospheric pressure and the residue was chromatographed on silica gel using CH₂Cl₂ as the eluent to give (-)-*endo*-brevicomine (**1**) as an oil (0.059 g, 76%); [α]_D²⁷ -77.4 ° (c 0.2, ether) [lit.,² [α]_D²¹ -75.9 ° (c 0.717, CHCl₃)]; δ _H (CDCl₃, 300 MHz) 0.99 (t, *J* 7.2, 3 H), 1.44 (s, 3 H), 1.52-2.00 (m, 8 H), 4.00 (dt, *J* 7.0, 4.0, 2 H), and 4.22 (m, 1 H); δ _C (CDCl₃, 75 MHz) 10.93, 17.52, 21.88, 23.63, 24.99, 34.44, 76.53, 81.68, and 106.99.

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Graphical Abstract

